

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 21-107

ADMINISTRATIVE DOCUMENTS

Executive CAC
October 12, 1999

Committee:

Joseph DeGeorge, Ph.D., HFD 024, Chair
Joseph Contrera, Ph.D., HFD-900, Member
Abby Jacobs, Ph.D., HFD-540, Alternate Member
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Author of Draft: Ke Zhang, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA #: 21,107

Drug Name: Alosetron Hydrochloride / GR 68755

Sponsor: Glaxo Wellcome, Inc.

Background:

The preliminary report of the mouse carcinogenicity study was submitted in the initial submission of IND. This study was reviewed on April 16, 1996 (Pharmacology review) and discussed at Executive CAC meeting on April 23, 1996. The dose selection was considered adequate and this study was acceptable. Sponsor submitted the final report of the study in NDA 21,107. GR 68755 was negative in the genotoxicity testing which included Ames test, in vitro chromosome aberration test in human lymphocytes, unscheduled DNA synthesis test in rat hepatocytes, mouse lymphoma cell assay, and rat micronucleus test. GR 62202, an intermediate in the synthesis of GR 68755, was positive in Ames test with one strain of *S. typhimurium*, TA 98 at concentrations of (g/plate in the absence of S9 and (g/plate in the presence of S9. However, it was negative with strain TA 1537 as well as strains TA 1535 and TA 100. Structurally, this intermediate is not similar to any of the known metabolites of the parent drug.

Mouse Carcinogenicity Study:

In this study, mice (B6C3F1) were treated with GR 68755 via drinking water at 0 (water), 0 (vehicle), 1, 5.5, and 30 mg/kg/day for 94/95 weeks in males and 104/105 weeks in females. There were no treatment related clinical signs of toxicity. Mortality rate was comparable in control and treatment groups. The body weight in high dose females was 91.4% of the control. Historical control data from the testing laboratory are not available.

Higher incidences of Harderian gland adenoma and liver cell tumors were found in the treated males and females, respectively.

The incidence of Harderian gland adenoma in males was 2, 2, 8, 7, and 6 in the control 1 (water), control 2 (vehicle), low, mid, and high dose groups, respectively. The incidence of hepatocellular adenoma in females was 2, 7, 11, 11, and 10 in the control1 (water), control2 (vehicle), low, mid, and high dose groups, respectively. The incidence of hepatocellular carcinoma in females was 1, 1, 6, 5, and 4 in the control 1 (water), control 2 (vehicle), low, mid, and high dose groups, respectively. The mean background incidence of Harderian gland adenoma in males was $7.73 \pm 3.9\%$ (range: _____). The mean background incidences of hepatocellular adenoma and carcinoma in females were $55.0 \pm 21.2\%$ (range: _____) and $19.7 \pm 12.8\%$ (range: _____), respectively. These background incidences were obtained from the NTP database. The increased incidences of Harderian gland adenoma and liver cell tumors are not dose related and within the background incidence. The increased incidences were not statistically significant by the trend test. The increased incidences in each of the treatment groups were not significantly (pairwise test) different from the incidences in the vehicle control group. Therefore, these are not considered biologically significant.

Treatment with GR 68755 produced benign interstitial cell tumor of the testes in a dose dependent manner (0, 0, 1, 1, and 2 for control 1 (water), control 2 (vehicle), low, mid, and high dose groups, respectively). A single incidence of malignant interstitial cell tumor in a mid dose male (none in the controls) was also observed. The combined incidences of benign and malignant tumors are 0, 0, 1, 2, and 2 in the control1 (water), control2 (vehicle), low, mid, and high dose groups, respectively. The increased incidences were not statistically significant by the trend test. The increased incidences in each of the treatment groups were not significantly (pairwise test) different from the incidences in the vehicle control group.


Executive CAC Recommendations and Conclusions:

1. The Committee felt in general that the results were either negative or equivocal. They expressed some concern about the increased incidence of the hepatocellular adenoma and carcinoma in female mice. While there is no increase of such tumors in the rat carcinogenicity study, there is some concern about the mutagenic potential of the intermediate _____.
2. The Committee recommended that the Division investigate (a) whether any of the metabolites of the parent drug is structurally similar to this intermediate and (b) whether this intermediate is present as an impurity in the drug product.

Further examination of the information in the NDA revealed the following: (a) none of the known metabolites of GR 68755 is structurally similar to _____ and (b) _____ which is below qualification threshold of _____ (Guideline for Industry: Impurities in New Drug Substance, ICH Q3A, January 1996). The recommended human dose is 1 mg b.i.d.

3. The Committee expressed concern regarding the lack of historical control data from the testing laboratory.

4. The study is adequate and acceptable. The Committee concluded that there was no evidence for tumorigenicity relevant to humans.

 10/18/99
✓ Joseph DeGeorge, Ph.D.
Chair, Executive CAC

cc:\n
/Division File, HFD-180
/HFD-181/CSO
/Dr. Choudary, HFD-180
/Dr. Zhang, HFD-180
/ASeifried, HFD

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA
Number: 21107 Trade Name: LOTIRONEX (ALOSETRON HCL) 1MG TABLETS
Supplement
Number: Generic Name: ALOSETRON HCL
Supplement
Type: Dosage Form: Tablet; Oral
Regulatory
Action: PN Proposed
Indication: treatment of irritable bowel syndrome (IBS) in female
patients whose primary bowel symptom is diarrhea

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No data was submitted for this indication, however, plans or ongoing studies exist for pediatric patients

What are the INTENDED Pediatric Age Groups for this submission?

 NeoNates (0-30 Days) Children (25 Months-12 years)
 Infants (1-24 Months) Adolescents (13-16 Years)

Label Adequacy Inadequate for ALL pediatric age groups
Formulation Status -
Studies Needed -
Study Status -

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

2/19/00-firm has requested a waiver of the 0-6 yr age group, and has submitted a PPSR for the other age groups.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER,
KATI JOHNSON

Signature

/S/

Date

1/19/00

1.4. Debarment Certification

from 1.1 volume
SD = 6.29.99

NDA 21-107

New Drug Application
Alosetron Hydrochloride Tablets

DEBARMENT CERTIFICATION

Glaxo Wellcome hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.



Charles E. Mueller
Head, Clinical Compliance
World Wide Compliance

20 MAY 99

Date

EXCLUSIVITY SUMMARY FOR NDA # 21-107 SUPPL #

Trade Name Lotronex Tablets Generic Name alosetron

Applicant Name Glaxo Wellcome Inc. HFD # 180

Approval Date If Known 2/9/00

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES / ☒ / NO / ☐ /

b) Is it an effectiveness supplement?

YES / ☐ / NO / ☒ /

If yes, what type? (SE1, SE2, etc.)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / ☒ / NO / ☐ /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / X / NO / /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

NO

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /_X_/

If yes, NDA #_____. Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES / / NO / X /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /__X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1

YES /___/

NO /___/

Investigation #2

YES /___/

NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1

YES /___/

NO /___/

Investigation #2

YES /___/

NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):
